=> fil reg; d stat que l8; fil capl; d que nos l9

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DICTIONARY FILE UPDATES: 15 MAR 2001 HIGHEST RN 327592-83-6

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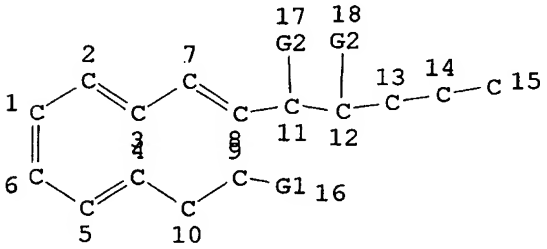
Structure search limits have been increased. See HELP SLIMIT for details.

L1 STR



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NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE
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SEARCH TIME: 00.00.03

FILE 'CAPLUS' ENTERED AT 15:32:14 ON 16 MAR 2001
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FILE COVERS 1967 - 16 Mar 2001 VOL 134 ISS 13
Searched by Barb O'Bryen, STIC 308-4291

FILE LAST UPDATED: 15 Mar 2001 (20010315/ED)

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L9          22 SEA FILE=CAPLUS ABB=ON  L8
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=> fil medl ipa biosis embase uspat; d que nos l10

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FILE 'IPA' ENTERED AT 15:32:31 ON 16 MAR 2001
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FILE 'USPATFULL' ENTERED AT 15:32:31 ON 16 MAR 2001
CA INDEXING COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)
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L10          3 SEA L8
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FILE 'CAPLUS' ENTERED AT 15:32:37 ON 16 MAR 2001
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FILE 'USPATFULL' ENTERED AT 15:32:37 ON 16 MAR 2001
CA INDEXING COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L9
PROCESSING COMPLETED FOR L10
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Searched by Barb O'Bryen, STIC 308-4291

L12 23 DUP REM L9 L10 (2 DUPLICATES REMOVED)
ANSWERS '1-22' FROM FILE CAPLUS
ANSWER '23' FROM FILE USPATFULL

=> d ibib abs hitstr l12 1-23; fil cao; d que nos l11; fil hom

L12 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
ACCESSION NUMBER: 1997:492901 CAPLUS
DOCUMENT NUMBER: 127:156724
TITLE: Lipoxin compounds, and preparation thereof, for modulation of inflammation related to columnar epithelia
INVENTOR(S): Madara, James L.; Serhan, Charles N.; Colgan, Sean P.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 19 pp. Cont.-in-part of U.S. Ser. No. 84,311, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

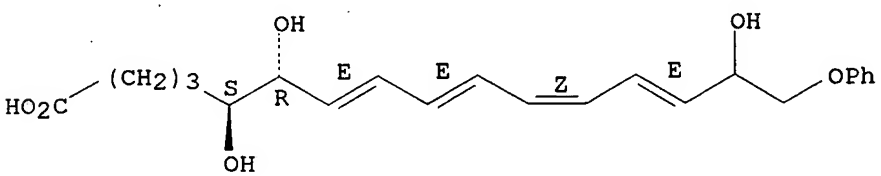
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5650435	A	19970722	US 1994-268049	19940629
US 6100296	A	20000808	US 1997-806278	19970225
US 6177468	B1	20010123	US 2000-496717	20000202
PRIORITY APPLN. INFO.:			US 1991-677388	19910401
			US 1991-748349	19910822
			US 1993-84311	19930629
			US 1994-268049	19940629
			US 1997-806278	19970225
			US 1997-955860	19971021

AB Pharmaceutical compns. contg. lipoxin compds. and therapeutic uses for the compds. in treating or preventing a disease or condition assocd. with columnar epithelial inflammation are provided. Also disclosed are methods for screening for compds. useful in preventing columnar epithelial inflammation. The compds. include lipoxin A4 and analogs thereof. Compds. were tested for their ability to inhibit neutrophil transmigration on epithelial cells. Prepn. of lipoxin compds. is also described.

IT **193279-94-6 193611-38-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipoxin compds., and prepn. thereof, for modulation of inflammation related to columnar epithelia)

RN 193279-94-6 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, (5S,6R,7E,9E,11Z,13E)-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

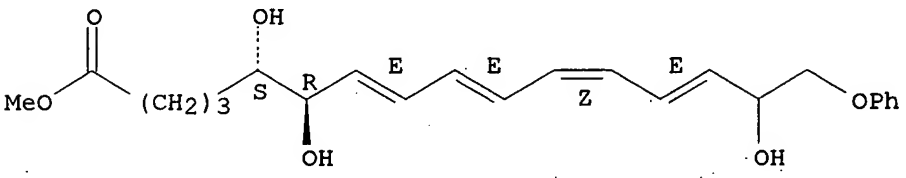


RN 193611-38-0 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, methyl ester, (5S,6R,7E,9E,11Z,13E)-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

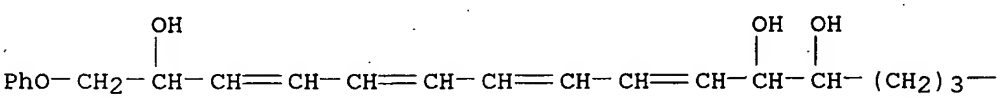


L12 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
ACCESSION NUMBER: 1995:795408 CAPLUS
DOCUMENT NUMBER: 124:8499
TITLE: Lipoxin compounds
INVENTOR(S): Serhan, Charles N.
PATENT ASSIGNEE(S): Brigham and Women's Hospital, USA
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5441951	A	19950815	US 1994-260030	19940615
US 5648512	A	19970715	US 1995-453125	19950531
US 6048897	A	20000411	US 1996-712610	19960913
PRIORITY APPLN. INFO.:			US 1993-77300	19930615
			US 1994-260030	19940615
			US 1995-453125	19950531

OTHER SOURCE(S): MARPAT 124:8499
AB Compds. having the active site of natural lipoxins, but a longer tissue half-life are disclosed. These mols. are useful for treating vasoconstrictive, inflammatory, myeloid suppressive, cardiovascular, and gastrointestinal diseases.
IT **161718-15-6P 161718-22-5P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(lipoxin analogs with longer tissue half-life)
RN 161718-15-6 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

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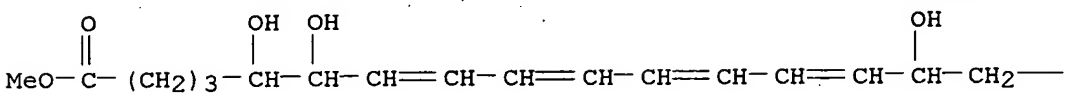
RN 161718-22-5 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, methyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

—OPh

L12 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:666685 CAPLUS
DOCUMENT NUMBER: 133:256820
TITLE: Lipoxin compounds and their use
INVENTOR(S): Serhan, Charles N.
PATENT ASSIGNEE(S): Brigham and Women's Hospital, USA
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000055109	A1	20000921	WO 2000-US6583	20000314

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1999-125209 19990318

AB Aspirin (ASA) triggers a switch in the biosynthesis of lipid mediators, inhibiting prostanoid prodn. and initiating 15-epi-lipoxin generation, through the acetylation of cyclooxygenase II. Results of expts. indicated that the inhibitory actions of aspirin-triggered lipoxins (ATL) are both tissue- and delivery site-dependent and are the first to show that stable analogs of ATL inhibit acute inflammation at sites distant from the point of delivery. Since ATL stable analogs were designed as mimetics to incorporate the native aspirin-triggered structural features, the findings provide new tools to examine endogenous anti-inflammatory pathways as well as avenues to approach the development of both topical and i.v. anti-PMN therapies.

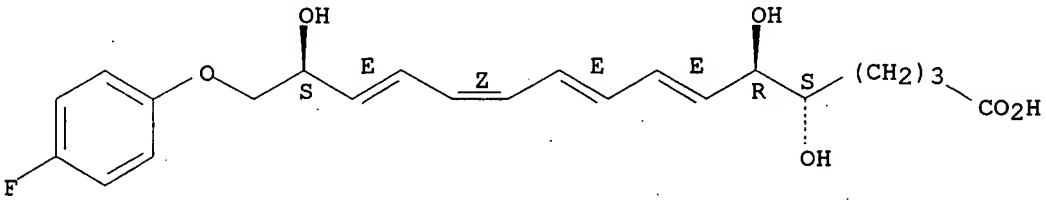
IT **228549-33-5**, ATLa2
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(aspirin-triggered lipoxins in inflammation inhibition and drug delivery)

RN 228549-33-5 CAPLUS

CN 7,9,11,13-Hexadecatetraenoic acid, 16-(4-fluorophenoxy)-5,6,15-trihydroxy-, (5S,6R,7E,9E,11Z,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 3

REFERENCE(S):
(1) Brigham & Women'S Hospital; WO 9811049 A 1998 CAPLUS
(2) Takano, T; 1998, 21, P41 CAPLUS
(3) Takano, T; J CLIN INVEST 1998, V101(4), P819 CAPLUS

L12 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:666595 CAPLUS

DOCUMENT NUMBER: 133:247276

TITLE: Use of lipoxin compounds for inhibiting of TNF-.alpha.-initiated neutrophil response

INVENTOR(S): Serhan, Charles N.

PATENT ASSIGNEE(S): Brigham and Women's Hospital, USA

SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000054767	A1	20000921	WO 2000-US6582	20000314

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1999-125205 19990318

OTHER SOURCE(S): MARPAT 133:247276

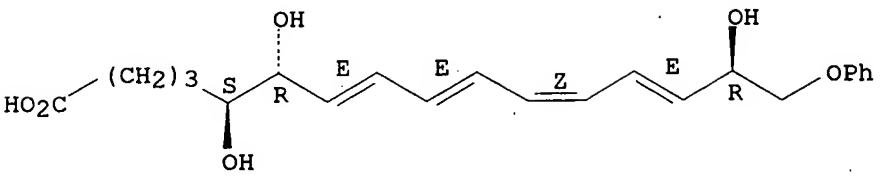
AB The impact of lipoxin A4 (LXA4) and aspirin-triggered-lipoxins (ATL) was investigated in tumor necrosis factor (TNF.alpha.)-initiated neutrophil (PMN) responses in vitro and in vivo using metabolically stable LX analogs. At concns. as low as 1-10 nM, the LXA4 and ATL analogs each inhibited TNF.alpha.-stimulated superoxide anion generation and IL-1.beta. release by human PMN.

IT **171030-12-9**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipoxin compds. for inhibiting of TNF-.alpha.-initiated neutrophil response)

RN 171030-12-9 CAPLUS

CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 7
REFERENCE(S):
(1) Brigham & Women'S Hospital; WO 9429262 A 1994 CAPLUS
(2) Brigham & Women'S Hospital; WO 9501179 A 1995 CAPLUS
(3) Brigham & Women'S Hospital; WO 9811049 A 1998 CAPLUS
(5) Serhan, C; US 5441951 A 1995 CAPLUS
(6) Takano, T; JOURNAL OF CLINICAL INVESTIGATIONS 1998, V101(4), P819 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:666589 CAPLUS
DOCUMENT NUMBER: 133:232831
TITLE: Lipoxin analogs for regulation of phospholipase D activity, and therapeutic use thereof
INVENTOR(S): Serhan, Charles N.
PATENT ASSIGNEE(S): Brigham and Women's Hospital, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000054761	A2	20000921	WO 2000-US6669	20000314

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1999-125194 19990318
OTHER SOURCE(S): MARPAT 133:232831

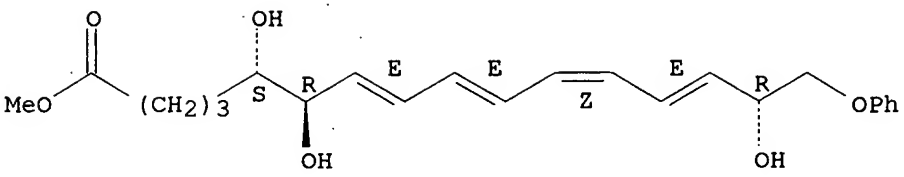
AB Lipoxin analogs are provided for modulating diseases and conditions assocd. with phospholipase D activity, including those assocd. with phospholipase D-initiated superoxide generation or degranulation activity. The effect of 15-epi-LXA4 in polyisoprenylphosphate signaling was examd. 15-Epi-LXA4 inhibited LTB4-stimulated phospholipase D activity and superoxide generation.

IT **171030-14-1**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(lipoxin analogs for regulation of phospholipase D activity, and therapeutic use)

RN 171030-14-1 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, methyl ester, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

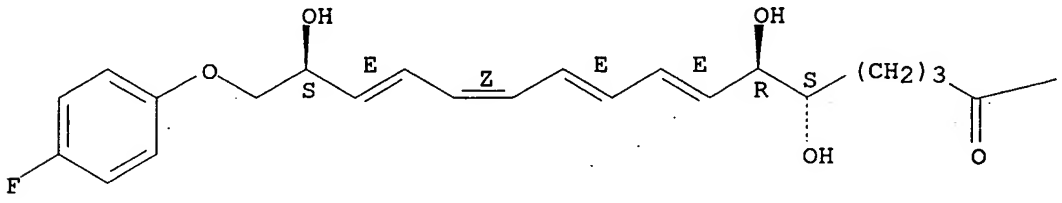
Searched by Barb O'Bryen, STIC 308-4291



IT **205176-29-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipoxin analogs for regulation of phospholipase D activity, and therapeutic use)
RN 205176-29-0 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 16-(4-fluorophenoxy)-5,6,15-trihydroxy-, methyl ester, (5S,6R,7E,9E,11Z,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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L12 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:198492 CAPLUS
DOCUMENT NUMBER: 133:3608
TITLE: Lipoxin A4 Analogues Inhibit Leukocyte Recruitment to Porphyromonas gingivalis: A Role for Cyclooxygenase-2 and Lipoxins in Periodontal Disease
AUTHOR(S): Pouliot, Marc; Clish, Clary B.; Petasis, Nicos A.; Van Dyke, Thomas E.; Serhan, Charles N.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury Department of Anesthesiology Perioperative and Pain Medicine Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Biochemistry (2000), 39(16), 4761-4768
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The potential involvement of the inducible cyclooxygenase isoform (COX-2) and the role of novel lipid mediators were investigated in the pathogenesis of periodontal disease. Crevicular fluids from localized juvenile periodontitis (LJP) patients contained prostaglandin (PG)E2 and 5-lipoxygenase-derived products, leukotriene B4, and the biosynthesis

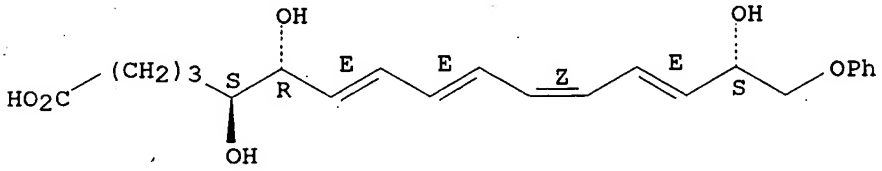
interaction product, lipoxin (LX)A4. Neutrophils from peripheral blood of LJP patients, but not from asymptomatic donors, also generated LXA4, suggesting a role for this immunomodulatory mol. in periodontal disease. To characterize host responses of interest to periodontal pathogens, P. gingivalis was introduced within murine dorsal air pouches. In the air pouch cavity, P. gingivalis elicited leukocyte infiltration, concomitant with elevated PGE2 levels in the cellular exudates, and upregulated COX-2 expression in infiltrated leukocytes. In addn., human neutrophils exposed to P. gingivalis also upregulated COX-2 expression. Blood borne P. gingivalis gave increases in the murine tissue levels of COX-2 mRNA assocd. with both heart and lungs, supporting a potential role for this oral pathogen in the evolution of systemic events. The administration of metabolically stable analogs of LX and of aspirin-triggered LX potently blocked neutrophil traffic into the dorsal pouch cavity and lowered PGE2 levels within exudates. These results identify thus PMN as an addnl. and important source of PGE2 in periodontal tissues. Moreover, they provide evidence for a novel protective role for LX in periodontitis, limiting further PMN recruitment and PMN-mediated tissue injury that can lead to loss of inflammatory barriers that prevent systemic tissue invasion of oral microbial pathogens.

IT **230954-56-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipoxin A4 analogs inhibit leukocyte recruitment to Porphyromonas gingivalis in periodontal disease)

RN 230954-56-0 CAPLUS

CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, (5S,6R,7E,9E,11Z,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 58
REFERENCE(S):
(1) Abramson, M; J Periodont Res 1992, V27, P539 CAPLUS
(2) Albers, H; Dtsch Zahnarztl Z 1979, V34, P440 CAPLUS
(3) Assuma, R; J Immunol 1998, V160, P403 CAPLUS
(4) Babior, B; Blood 1984, V64, P959 CAPLUS
(5) Borgeat, P; Clin Biochem 1990, V23, P459 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

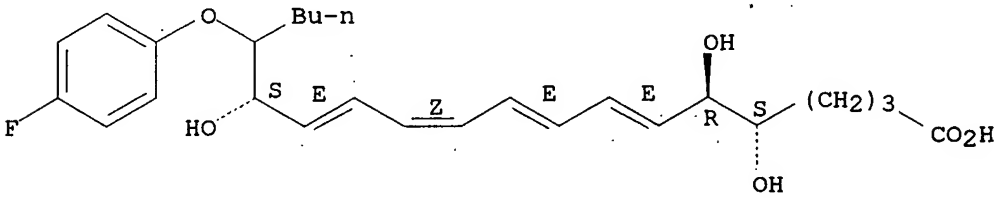
L12 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:146214 CAPLUS
DOCUMENT NUMBER: 132:303164
TITLE: Cutting edge: lipoxin (LX) A4 and aspirin-triggered 15-Epi-LXA4 block allergen-induced eosinophil trafficking
AUTHOR(S): Bandeira-Melo, Christianne; Bozza, Patricia T.; Diaz, Bruno L.; Cordeiro, Renato S. B.; Jose, Peter J.; Martins, Marco A.; Serhan, Charles N.
CORPORATE SOURCE: Department of Physiology and Pharmacodynamics, Oswaldo Cruz Institute, Rio de Janeiro, Brazil
SOURCE: J. Immunol. (2000), 164(5), 2267-2271
Searched by Barb O'Bryen, STIC 308-4291

CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tissue eosinophilia prevention represents one of the primary targets to new anti-allergic therapies. As lipoxin A4 (LXA4) and aspirin-triggered 15-epi-LXA4 (ATL) are emerging as endogenous "stop signals" produced in distinct pathologies including some eosinophil-related pulmonary disorders, the authors evaluated the impact of in situ LXA4/ATL metabolically stable analogs on allergen-induced eosinophilic pleurisy in sensitized rats. LXA4/ATL analogs dramatically blocked allergic pleural eosinophil influx, while concurrently increasing circulating eosinophilia, inhibiting the earlier edema and neutrophilia assocd. with allergic reaction. The mechanisms underlying this LXA4/ATL-driven allergic eosinophilia blockade was independent of mast cell degranulation and involved LXA4/ATL inhibition of both IL-5 and eotaxin generation, as well as platelet activating factor action. These findings reveal LXA4/ATL as a novel class of endogenous anti-allergic mediators, capable of preventing local eosinophilia.

IT **265316-15-2**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiallergic impact of lipoxin (LX) A4 and aspirin-triggered 15-Epi-LXA4 analogs in eosinophilic pleurisy)
RN 265316-15-2 CAPLUS
CN 7,9,11,13-Eicosatetraenoic acid, 16-(4-fluorophenoxy)-5,6,15-trihydroxy-, (5S,6R,7E,9E,11Z,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 36
REFERENCE(S):
(1) Alves, A; Eur J Pharmacol 1996, V312, P89 CAPLUS
(4) Clish, C; Proc Natl Acad Sci USA 1999, V96, P8247 CAPLUS
(7) Edenius, C; FEBS Lett 1990, V272, P25 CAPLUS
(8) Gewirtz, A; Am J Physiol 1999, V276, PC988 CAPLUS
(9) Gewirtz, A; J Clin Invest 1998, V101, P1860 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:138534 CAPLUS
DOCUMENT NUMBER: 132:278030
TITLE: Cutting edge: lipoxins rapidly stimulate non-phlogistic phagocytosis of apoptotic neutrophils by monocyte-derived macrophages
AUTHOR(S): Godson, Catherine; Mitchell, Siobhan; Harvey, Killeen; Petasis, Nicos A.; Hogg, Nancy; Brady, Hugh R.
CORPORATE SOURCE: Centre for Molecular Inflammation and Vascular Research, Mater Misericordiae Hospital and Department of Medicine and Therapeutics, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, 7, Ire.
Searched by Barb O'Bryen, STIC 308-4291

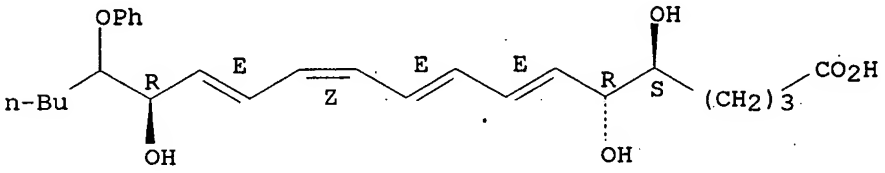
SOURCE: J. Immunol. (2000), 164(4), 1663-1667
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lipoxins (LX) are lipoxygenase-derived eicosanoids generated during inflammation. LX inhibit polymorphonuclear neutrophil (PMN) chemotaxis and adhesion and are putative braking signals for PMN-mediated tissue injury. Here, the authors report that LXA4 promotes another important step in the resoln. phase of inflammation, namely, phagocytosis of apoptotic PMN by monocyte-derived macrophages (M.phi.). LXA4 triggered rapid, concn.-dependent uptake of apoptotic PMN. This bioactivity was shared by stable synthetic LXA4 analogs but not by other eicosanoids tested. LXA4-triggered phagocytosis did not provoke IL-8 or monocyte chemoattractant protein-1 release. LXA4-induced phagocytosis was attenuated by anti-CD36, .alpha.v.beta.3, and CD18 mAbs. LXA4-triggered PMN uptake was inhibited by pertussis toxin and by 8-bromo-cAMP and was mimicked by Rp-cAMP, a protein kinase A inhibitor. LXA4 attenuated PGE2-stimulated protein kinase A activation in M.phi.. These results suggest that LXA4 is an endogenous stimulus for PMN clearance during inflammation and provide a novel rationale for using stable synthetic analogs as anti-inflammatory compds. in vivo.

IT **260064-29-7**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipoxins rapidly stimulate non-phlogistic phagocytosis of apoptotic neutrophils by monocyte-derived macrophages)

RN 260064-29-7 CAPLUS
CN 7,9,11,13-Eicosatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 31
REFERENCE(S):
(1) Asch, A; Science 1993, V262, P1436 CAPLUS
(2) Chiang, N; J Pharmacol Exp Ther 1998, V287, P779 CAPLUS
(3) Clish, C; Proc Natl Acad Sci USA 1999, V96, P8247 CAPLUS
(4) Colgan, S; J Clin Invest 1993, V92, P75 CAPLUS
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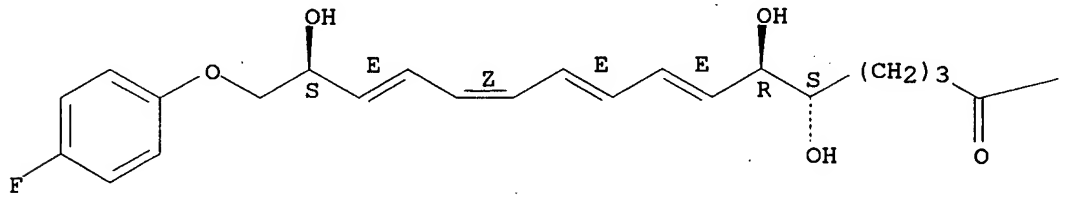
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:228388 CAPLUS
DOCUMENT NUMBER: 133:16222
TITLE: Activation of lipoxin A4 receptors by aspirin-triggered lipoxins and select peptides evokes ligand-specific responses in inflammation
AUTHOR(S): Chiang, Nan; Fierro, Iolanda M.; Gronert, Karsten; Serhan, Charles N.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative

and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: J. Exp. Med. (2000), 191(7), 1197-1207
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lipoxin (LX) A4 and aspirin-triggered LX (ATL) are endogenous lipids that regulate leukocyte trafficking via specific LXA4 receptors (ALXRs) and mediate antiinflammation and resoln. ATL analogs dramatically inhibited human neutrophil [polymorphonuclear leukocyte (PMN)] responses evoked by a potent necrotactic peptide derived from mitochondria as well as a rogue synthetic chemotactic peptide. These bioactive lipid analogs and small peptides each selectively competed for specific 3H-LXA4 binding with recombinant human ALXR, and its N-glycosylation proved essential for peptide but not LXA4 recognition. Chimeric receptors constructed from receptors with opposing functions, namely ALXR and leukotriene B4 receptors (BLTs), revealed that the seventh transmembrane segment and adjacent regions of ALXR are essential for LXA4 recognition, and addnl. regions of ALXR are required for high affinity binding of the peptide ligands. Together, these findings are the first to indicate that a single 7-transmembrane receptor can switch recognition as well as function with certain chemotactic peptides to inhibitory with ATL and LX (lipid ligands). Moreover, they suggest that ALXR activation by LX or ATL can protect the host from potentially deleterious PMN responses assocd. with innate immunity as well as direct effector responses in tissue injury by recognition of peptide fragments.
IT **205176-29-0**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(lipoxin A4 receptors activation by aspirin-triggered lipoxins and select peptides evokes ligand-specific responses in inflammation)
RN 205176-29-0 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 16-(4-fluorophenoxy)-5,6,15-trihydroxy-, methyl ester, (5S,6R,7E,9E,11Z,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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(3) Castano, A; Science 1995, V269, P223 CAPLUS
Searched by Barb O'Bryen, STIC 308-4291

(4) Chiang, N; J Clin Invest 1999, V104, P309 CAPLUS
(5) Clish, C; Proc Natl Acad Sci USA 1999, V96, P8247 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:354308 CAPLUS
DOCUMENT NUMBER: 134:4031
TITLE: A novel polyisoprenyl phosphate signaling cascade in human neutrophils
AUTHOR(S): Levy, Bruce D.; Serhan, Charles N.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesia, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Ann. N. Y. Acad. Sci. (2000), 905(Lysophospholipids and Eicosanoids in Biology and Pathophysiology), 69-80
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

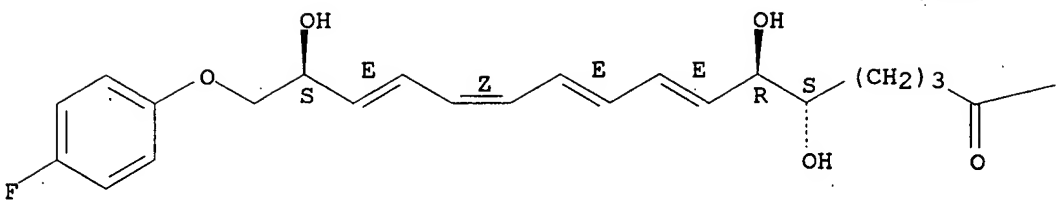
AB Activation of neutrophil (PMN) surface receptors can evoke inflammation and tissue injury via aberrant release of excess effectors. The mol. mechanisms involved in host protection and control of PMN responses have yet to be defined. As Billah and coworkers (1989) and Exton (1997), for example, have pointed out, phospholipase D (PLD) signaling is known to play a pivotal role in PMN activation. Here, we detd. the relationship between polyisoprenyl phosphate (PIPP) remodeling and PLD signaling and their impact in activation of PMN receptors by "proinflammatory" (leukotriene B4), and "anti-inflammatory" (aspirin-triggered lipoxin A4) ligands. Activation of the leukotriene B4 receptor initiated a rapid (within seconds) decrement in presqualene diphosphate (PSDP), activation of PLD and prodn. of superoxide anions. This contrasts with activation of the LXA4 receptor by an aspirin-triggered lipoxin A4 mimetic that before leukotriene B4 gave an inverse relationship with rapidly increasing PSDP levels, and inhibition of both PLD activity and superoxide generation. PSDP proved to be a potent and direct-acting inhibitor of PLD (rhPLD1b: Ki = 5.9 nM), a property not shared by structurally related endogenous lipids. This PIPP also interacted with Src homol. domains, selectively targeting SH2 and not SH3 domains. These results indicate a role for ligand-driven rapid PIPP remodeling as an early switch and "stop" signaling event that controls PMN. Moreover, they indicate that PSDP directly down-regulates PMN signaling events via select protein-targeted interactions controlling intracellular responses relevant in inflammation.

IT **205176-29-0**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(polyisoprenyl phosphate remodeling and phospholipase D signaling in relation to activation of leukotriene B4 receptor and lipoxin A4 receptor in neutrophils)

RN 205176-29-0 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 16-(4-fluorophenoxy)-5,6,15-trihydroxy-, methyl ester, (5S,6R,7E,9E,11Z,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 24
REFERENCE(S):
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(5) Exton, J; J Biol Chem 1997, V272, P15579 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:507837 CAPLUS
DOCUMENT NUMBER: 131:266744
TITLE: Local and systemic delivery of a stable aspirin-triggered lipoxin prevents neutrophil recruitment in vivo
AUTHOR(S): Clish, Clary B.; O'Brien, Jennifer A.; Gronert, Karsten; Stahl, Gregory L.; Petasis, Nicos A.; Serhan, Charles N.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1999), 96(14), 8247-8252
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aspirin (ASA) triggers a switch in the biosynthesis of lipid mediators, inhibiting prostanoid prodn. and initiating 15-epi-lipoxin generation through the acetylation of cyclooxygenase II. These aspirin-triggered lipoxins (ATL) may mediate some of ASA's beneficial actions and therefore are of interest in the search for novel antiinflammatories that could manifest fewer unwanted side effects. Here, we report that design modifications to native ATL structure prolong its biostability in vivo. In mouse whole blood, ATL analogs protected at carbon 15 [15(R/S)-methyl-lipoxin A4 (ATLa1)] and the omega end [15-epi-16-(para-fluoro)-phenoxy-LXA4 (ATLa2)] were recoverable to .apprxeq.90 and 100% at 3 h, resp., compared with a .apprxeq.40% loss of native lipoxin A4. ATLa2 retains bioactivity and, at levels as low as .apprxeq.24 nmol/mouse, potently inhibited tumor necrosis factor-.alpha.-induced leukocyte recruitment into the dorsal air pouch. Inhibition was evident by either local intra-air pouch delivery (.apprxeq.77% inhibition) or systemic

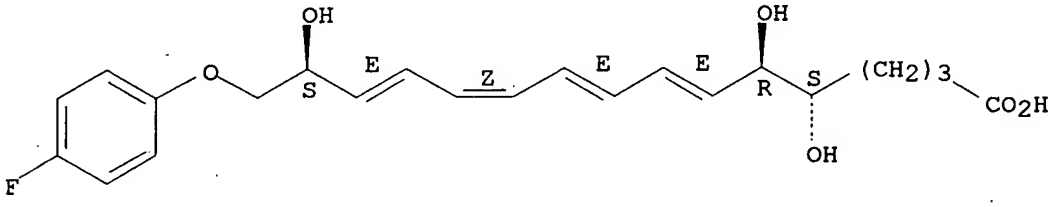
delivery by i.v. injection (.apprxeq.85% inhibition) and proved more potent than local delivery of ASA. Rank order for inhibiting polymorphonuclear leukocyte infiltration was: ATLa2 (10 .mu.g, i.v.) .apprxeq.ATLa2 (10 .mu.g, local) .apprxeq.dexamethasone (10 .mu.g, local) >ASA (1.0 mg, local). Applied topically to mouse ear skin, ATLa2 also inhibited polymorphonuclear leukocyte infiltration induced by leukotriene B4 (.apprxeq.78% inhibition) or phorbol ester (.apprxeq.49% inhibition), which initiates endogenous chemokine prodn. These results indicate that this fluorinated analog of natural aspirin-triggered lipoxin A4 is bioavailable by either local or systemic delivery routes and is a more potent and precise inhibitor of neutrophil accumulation than is ASA.

IT **228549-33-5**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(structure on p. 8249; local and systemic delivery of a stable aspirin-triggered lipoxin prevents neutrophil recruitment in vivo)

RN 228549-33-5 CAPLUS

CN 7,9,11,13-Hexadecatetraenoic acid, 16-(4-fluorophenoxy)-5,6,15-trihydroxy-, (5S,6R,7E,9E,11Z,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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(6) Dahlen, S; Lipoxygenases and Their Products 1991, P235 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

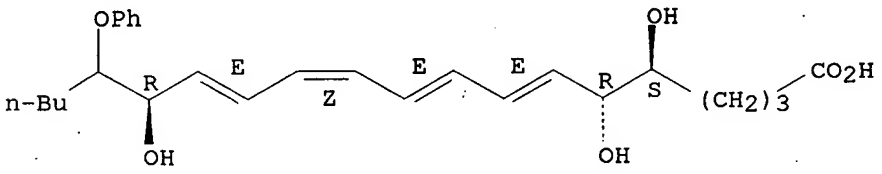
L12 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:797035 CAPLUS
DOCUMENT NUMBER: 132:189458
TITLE: Anti-inflammatory actions of lipoxin A4 stable analogs are demonstrable in human whole blood: modulation of leukocyte adhesion molecules and inhibition of neutrophil-endothelial interactions
AUTHOR(S): Filep, Janos G.; Zouki, Christine; Petasis, Nicos A.; Hachicha, Mohamed; Serhan, Charles N.
CORPORATE SOURCE: Research Center, Maisonneuve-Rosemont Hospital, Department of Medicine, University of Montreal, Montreal, PQ, Can.
SOURCE: Blood (1999), 94(12), 4132-4142
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
Searched by Barb O'Bryen, STIC 308-4291

AB The authors examd. in whole blood the actions of 2 lipoxin A4 (LXA4) stable analogs, 15-R/S-methyl-LXA4 and 16-phenoxy-LXA4, for their impact on the expression of adhesion mols. on human leukocytes and coronary artery endothelial cells (HCAEC) and on neutrophil adhesion to HCAEC in vitro. Both LXA4 analogs in nanomolar to micromolar concns. prevented shedding of L-selectin and downregulated CD11/CD18 expression on resting neutrophils, monocytes, and lymphocytes. Changes in CD11/CD18 expression were blocked by the mitogen-activated protein kinase kinase inhibitor PD98059. The LXA4 analogs also attenuated changes in L-selectin and CD11/CD18 expression evoked by platelet-activating factor (PAF), interleukin-8, or C-reactive protein-derived peptide 201-206 with IC50 values of 0.2 to 1.9 .mu.mol/L, whereas they did not affect lipopolysaccharide (LPS)- or tumor necrosis factor-.alpha.-stimulated expression of E-selectin and intercellular adhesion mol.-1 on HCAEC. These LXA4 analogs markedly diminished adhesion of neutrophils to LPS-activated HCAEC. Inhibition of adhesion was additive with function blocking anti-E-selectin and anti-L-selectin antibodies, but was not additive with anti-CD18 antibody. Combining LXA4 analogs with dexamethasone (100 nmol/L) almost completely inhibited PAF-induced changes in adhesion mol. expression on leukocytes and gave additive inhibition of neutrophil adhesion to HCAEC. Culture of HCAEC with dexamethasone, but not with LXA4 analogs, also decreased neutrophil attachment. Thus, LXA4 stable analogs modulate expression of both L-selectin and CD11/CD18 on resting and immunostimulated leukocytes and inhibit neutrophil adhesion to HCAEC by attenuating CD11/CD18 expression. These actions are additive with those of glucocorticoids and may represent a novel and potent regulatory mechanism by which LXA4 and aspirin-triggered 15-epi-LXA4 modulate leukocyte trafficking.

IT **260064-29-7**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-inflammatory actions of lipoxin A4 stable analogs in human whole blood are via modulation of leukocyte adhesion mols. and inhibition of neutrophil-endothelial interactions)

RN 260064-29-7 CAPLUS
CN 7,9,11,13-Eicosatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:274601 CAPLUS
DOCUMENT NUMBER: 131:68434
Searched by Barb O'Bryen, STIC 308-4291

TITLE: LXA4, aspirin-triggered 15-epi-LXA4, and their analogs selectively downregulate PMN azurophilic degranulation

AUTHOR(S): Gewirtz, Andrew T.; Fokin, Valery V.; Petasis, Nicos A.; Serhan, Charles N.; Madara, James L.

CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA, USA

SOURCE: Am. J. Physiol. (1999), 276(4, Pt. 1), C988-C994
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

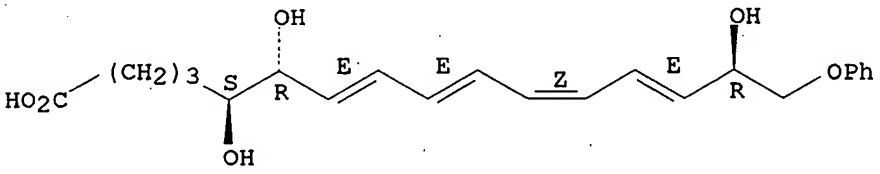
LANGUAGE: English

AB The eicosanoid lipoxin A4 (LXA4) is biosynthesized in vivo by cells present at inflammatory sites and appears to be an endogenous anti-inflammatory mediator. Further, in the presence of aspirin, the 15-epimer of LXA4 (15-epi-LXA4) is biosynthesized and may mediate some of aspirin's desirable bioactions. LXA4, 15-epi-LXA4, and their stable analogs inhibit inflammation in established animal models, indicating that these compds. may be useful for treating inflammatory disease states. To investigate the cellular mechanisms by which these lipid mediators downregulate inflammation, the authors investigated whether these eicosanoids could influence receptor-mediated degranulation of human neutrophils, an event thought to play a major causative role in several inflammatory disease states. LXA4, 15-epi-LXA4, and their stable analogs potently (IC50 <1 nM) and selectively downregulated neutrophil release of azurophilic granule contents but did not affect other neutrophil secretory functions. Thus, the cellular basis of action of these natural off-switches to inflammation appears to involve downregulation of neutrophil azurophilic granule release.

IT **171030-12-9 228549-33-5**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(LXA4 and aspirin-triggered 15-epi-LXA4 and their analogs selectively downregulate PMN azurophilic degranulation)

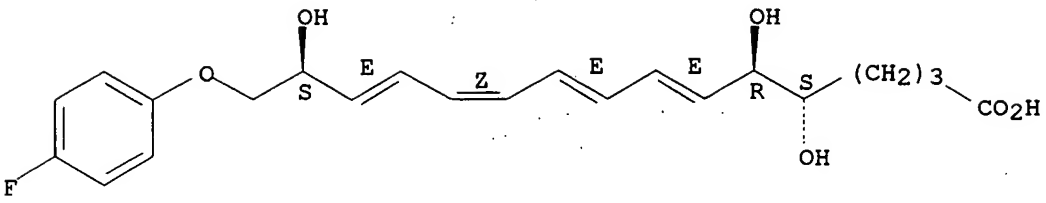
RN 171030-12-9 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 228549-33-5 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 16-(4-fluorophenoxy)-5,6,15-trihydroxy-, (5S,6R,7E,9E,11Z,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 37
REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:315716 CAPLUS
DOCUMENT NUMBER: 131:101234
TITLE: Polyisoprenyl phosphate (PIPP) signaling regulates phospholipase D activity: a "stop" signaling switch for aspirin-triggered lipoxin A4
AUTHOR(S): Levy, Bruce D.; Fokin, Valery V.; Clark, Joanna M.; Wakelam, Michael J. O.; Petasis, Nicos A.; Serhan, Charles N.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: FASEB J. (1999), 13(8), 903-911
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

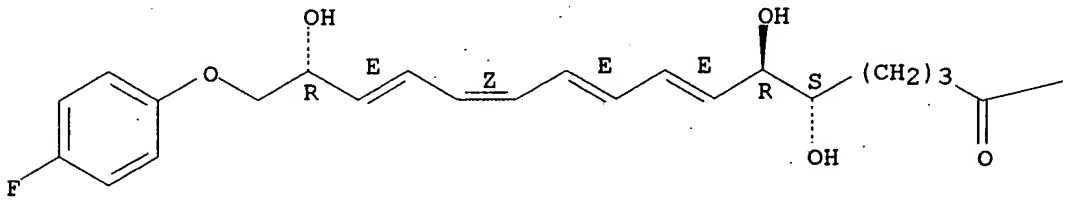
AB It is of wide interest to understand how opposing extracellular signals (pos. or neg.) are translated into intracellular signaling events. Receptor-ligand interactions initiate the generation of bioactive lipids by human neutrophils (PMN), which serve as signals to orchestrate cellular responses important in host defense and inflammation. The authors recently identified a novel polyisoprenyl phosphate (PIPP) signaling pathway and found that one of its components, presqualene diphosphate (PSDP), is a potent neg. intracellular signal in PMN that regulates superoxide anion generation by several stimuli, including phosphatidic acid. The authors detd. intracellular PIPP signaling by autocoids with opposing actions on PMN: leukotriene B4 (LTB4), a potent chemoattractant, and lipoxin A4 (LXA4), a "stop signal" for recruitment. LTB4 receptor activation initiated a rapid decrease in PSDP levels concurrent with activation of PLD and cellular responses. In sharp contrast, activation of the LXA4 receptor reversed LTB4-initiated PSDP remodeling, leading to an accumulation of PSDP and potent inhibition of both PLD and superoxide anion generation. Thus, an inverse relation was established for PSDP levels and PLD activity with two PMN ligands that evoke opposing responses. In addn., PSDP directly inhibited both isolated human recombinant (Ki = 6 nM) and plant (Ki = 20 nM) PLD. Together, these findings link PIPP remodeling to intracellular regulation of PMN function and suggest a role for PIPPs as lipid repressors in signal transduction, a novel mechanism that may also explain aspirin's suppressive actions in vivo in cell signaling.

Searched by Barb O'Bryen, STIC 308-4291

IT **230954-55-9 230954-56-0**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(increase in intracellular presqualene diphosphate levels and inhibition of phospholipase D activity in superoxide prodn. by human neutrophils by)
RN 230954-55-9 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 16-(4-fluorophenoxy)-5,6,15-trihydroxy-, methyl ester, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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RN 230954-56-0 CAPLUS
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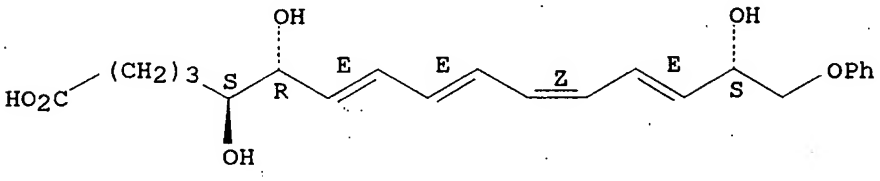
Absolute stereochemistry.
Double bond geometry as shown.



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REFERENCE(S):
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(4) Billah, M; J Biol Chem 1989, V264, P17069 CAPLUS
(6) Chiang, N; J Pharmacol Exp Ther 1998, V287, P779 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:180829 CAPLUS
DOCUMENT NUMBER: 128:252973
TITLE: Lipoxin compounds and their use in treating cell proliferative disorders
INVENTOR(S): Serhan, Charles N.
Searched by Barb O'Bryen, STIC 308-4291

PATENT ASSIGNEE(S): Brigham & Women's Hospital, USA
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9811049	A1	19980319	WO 1997-US16342	19970915
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6048897	A	20000411	US 1996-712610	19960913
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AU 723321	B2	20000824		
EP 927150	A1	19990707	EP 1997-941078	19970915
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PRIORITY APPLN. INFO.:
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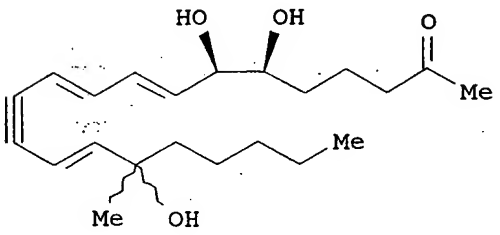

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AB Lipoxin analogs, e.g., I, having the active site of natural lipoxins but a longer tissue half-life, are prepd. Thus, I was prepd. via reaction of 3-methyl-3-(trimethylsilyloxy)-1-bromo-1-octene with (7E,9E,5S,6R)-Me 5,6-bis(tert-butyldimethylsilyloxy)-7,9-dodecadien-11-ynoate in benzene contg. propylamine and Pd(PPh3)4 and treating the product with BuN4Fin THF. In particular, 15-epi-lipoxins and their use in ameliorating undesired cell proliferation, which characterizes diseases such as cancer, are also disclosed. The prepd. compds. inhibited neutrophil adhesion to endothelial cells and their transmigration on epithelial cells. Among the prepd. compds., those with acetylenic groups were more stable than others; also the compd. that lacked a 15-OH group showed no biol. activity. [14,15-3H]LXA4 was prepd. and its specific binding to promyelocytic cells (HL-60) was compared with that of [14,15-3H]LTB4 and the results are essentially in agreement with values recently reported by Harada (1991). Bioassays of prepd. compds. were also carried out.

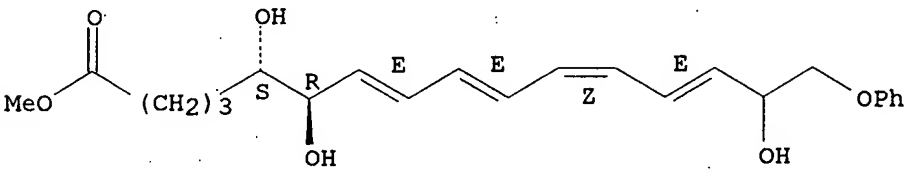
IT **193611-38-0P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of lipoxin analogs for treating cell proliferative disorders)

RN 193611-38-0 CAPLUS

Searched by Barb O'Bryen, STIC 308-4291

CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, methyl ester, (5S,6R,7E,9E,11Z,13E)-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L12 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:320841 CAPLUS
DOCUMENT NUMBER: 129:62611
TITLE: Pathogen-induced chemokine secretion from model intestinal epithelium is inhibited by lipoxin A4 analogs
AUTHOR(S): Gewirtz, Andrew T.; Mccormick, Beth; Neish, Andrew S.; Petasis, Nicos A.; Gronert, Karsten; Serhan, Charles N.; Madara, James L.
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, 30322, USA
SOURCE: J. Clin. Invest. (1998), 101(9), 1860-1869
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

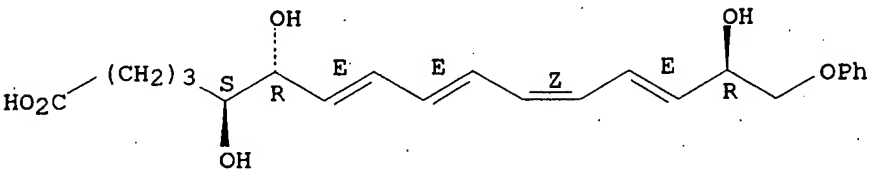
AB Enteric pathogens induce intestinal epithelium to secrete chemokines that direct movement of polymorphonuclear leukocytes. Mechanisms that might downregulate secretion of these proinflammatory chemokines and thus contain intestinal inflammation have not yet been elucidated. The antiinflammatory activities exhibited by the arachidonate metabolite lipoxin A4 (LXA4) suggests that this eicosanoid, which is biosynthesized in vivo at sites of inflammation, might play such a role. We investigated whether chemokine secretion could be regulated by stable analogs of LXA4. Monolayers of T84 intestinal epithelial cells were infected with Salmonella typhimurium, which elicits secretion of distinct apical (pathogen-elicited epithelial chemoattractant) and basolateral (IL-8) chemokines. Stable analogs of LXA4 inhibited S. typhimurium-induced (but not phorbol ester-induced) secretion of both IL-8 and pathogen-elicited epithelial chemoattractant. LXA4 stable analogs did not alter bacterial adherence to nor internalization by epithelia, indicating that LXA4 stable analogs did not block all signals that Salmonella typhimurium activates in intestinal epithelia, but likely led to attenuation of signals that mediate chemokine secretion. Inhibition of S. typhimurium-induced IL-8 secretion by LXA4 analogs was concn.- (IC50.apprx.1 nM) and time-dependent (maximal inhibition .apprx. 1 h). As a result of these effects, LXA4 stable analogs inhibited the ability of bacteria-infected epithelia to direct polymorphonuclear leukocyte movement. These data suggest that LXA4 and its stable analogs may be useful in downregulating active inflammation at mucosal surfaces.

IT **171030-12-9**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pathogen-induced chemokine secretion from model intestinal epithelium is inhibited by lipoxin A4 analogs)

RN 171030-12-9 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-,

(5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L12 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:121846 CAPLUS
DOCUMENT NUMBER: 128:252676
TITLE: Neutrophil-mediated changes in vascular permeability are inhibited by topical application of aspirin-triggered 15-epi-lipoxin A4 and novel lipoxin B4 stable analogs
AUTHOR(S): Takano, Tomoko; Clish, Clary B.; Gronert, Karsten; Petasis, Nicos; Serhan, Charles N.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesia, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, 02115, USA
SOURCE: J. Clin. Invest. (1998), 101(4), 819-826
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

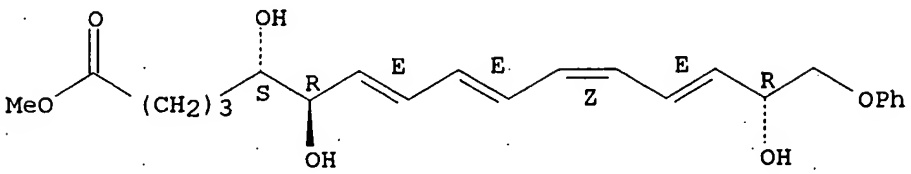
AB Neutrophil (PMN) activation is crit. in inflammation and reperfusion injury, suggesting that PMN-directed therapies may be of clin. use. Here, leukotriene B4 (LTB4)-induced PMN influx in ear skin was equiv. between 5-lipoxygenase knockout and wild-type mice. To explore actions of lipoxin (LX) in PMN-mediated tissue injury, we prepd. several novel LX stable analogs, including analogs of LXA4 and aspirin-triggered 15-epi-LXA4 as well as LXB4, and examd. their impact in PMN infiltration and vascular permeability. Each applied topically to mouse ears inhibited dramatically PMN-mediated increases in vascular permeability (IC50 range of 13-26 nmol) with a rank order of 15(R/S)-methyl-LXA4 > 16-para-fluoro-phenoxy-LXA4 .apprx. 5(S)-methyl-LXB4 .gtoreq. 16-phenoxy-LXA4 > 5(R)-methyl-LXB4. These LX mimetics were as potent as an LTB4 receptor antagonist, yet results from microphysiometry with mouse leukocytes indicated that they do not act as LTB4 receptor level antagonists. In addn., within 24 h of delivery, > 90% were cleared from ear biopsies. Neither IL-8, FMLP, C5a, LTD4, nor platelet-activating factor act topically to promote PMN influx. When applied with LTB4, PGE2 enhanced sharply both infiltration and vascular permeability, which were inhibited by a fluorinated stable analog of aspirin-triggered LX. These results indicate that mimetics of LXs and aspirin-triggered 15-epi-LXA4 are topically active in this model and are potent inhibitors of both PMN infiltration and PMN-mediated vascular injury.

IT **171030-14-1 205176-29-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neutrophil-mediated changes in vascular permeability inhibited by topical application of aspirin-triggered 15-epi-lipoxin A4 and novel lipoxin B4 analogs)

RN 171030-14-1 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, methyl

ester, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

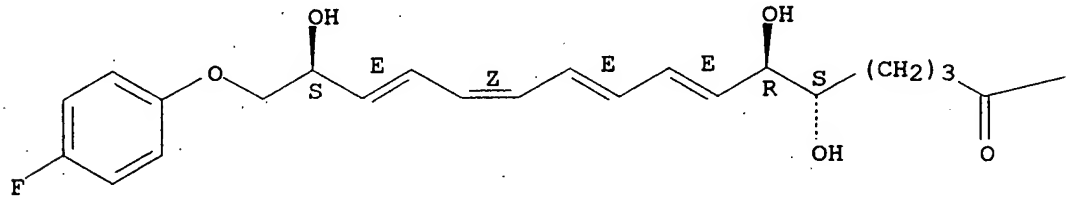
Absolute stereochemistry.
Double bond geometry as shown.



RN 205176-29-0 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 16-(4-fluorophenoxy)-5,6,15-trihydroxy-, methyl ester, (5S,6R,7E,9E,11Z,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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L12 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:581522 CAPLUS
DOCUMENT NUMBER: 127:257275
TITLE: Lipoxin A4 stable analogs inhibit leukocyte rolling and adherence in the rat mesenteric microvasculature: role of P-selectin
AUTHOR(S): Scalia, Rosario; Gefen, Jonathan; Petasis, Nicos A.; Serhan, Charles N.; Lefer, Allan M.
CORPORATE SOURCE: Dep. Physiology, Jefferson Medical College, Thomas Jefferson Univ., Philadelphia, PA, 19107-6799, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1997), 94(18), 9967-9972
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three different stable lipoxin A4 (LXA4) analogs (i.e., 16-phenoxy-LXA4-Me, 15-cyclohexyl-LXA4-Me, and 15-R/S-methyl-LXA4-Me) were studied of their ability to modulate leukocyte-endothelial cell interactions in the rat mesenteric microvasculature. Superfusion of the rat mesentery with 50 .mu.mol/L NG-nitro-L-arginine Me ester (L-NAME) caused a significant, time-dependent increase in leukocyte rolling (56.+-.8 cells/min; vs. control) and leukocyte adherence (12.5.+-.1.2

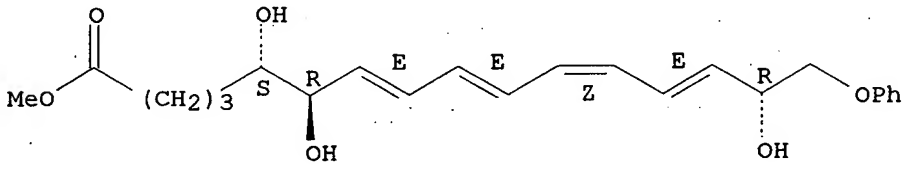
cells/100 .mu.m length of venule; vs. control) after 120 min of superfusion. Concomitant superfusion of the rat mesentery with 10 nmol/L of each of three lipoxin analogs consistently and markedly attenuated L-NAME-induced leukocyte rolling to 10.+-.4, 4.+-.1, and 32.+-.7 cells/min, and adherence to 4.+-.0.8, 1.1.+-.0.4, and 7.+-.0.7 cells/100 .mu.m length of venule (16-phenoxy-LXA4-Me, 15-cyclohexyl-LXA4-Me, and 15-R/S-methyl-LXA4-Me, resp.). No alterations of systemic blood pressure or mesenteric venular shear rates were obsd. in any group. Immunohistochem. up-regulation of P-selectin expression on intestinal venular endothelium was significantly increased after exposure to L-NAME, and this was significantly attenuated by these lipoxin analogs. Thus, in vivo superfusion of the rat mesentery with stable lipoxin analogs at 10 nmol/L reduces L-NAME-induced leukocyte rolling and adherence in the mesenteric rat microvasculature by attenuating P-selectin expression. This anti-inflammatory mechanism may represent a novel and potent regulatory action of lipoxins on the immune system.

IT **171030-14-1**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipoxin A4 stable analogs inhibit leukocyte rolling and adherence in rat mesenteric microvasculature)

RN 171030-14-1 CAPLUS

CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, methyl ester, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L12 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:196043 CAPLUS
DOCUMENT NUMBER: 126:291403
TITLE: Lipoxin A4 stable analogs are potent mimetics that stimulate human monocytes and THP-1 cells via a G-protein-linked lipoxin A4 receptor
AUTHOR(S): Maddox, Jane F.; Hachicha, Mohamed; Takano, Tomoko; Petasis, Nicos A.; Fokin, Valery V.; Serhan, Charles N.
CORPORATE SOURCE: Cent. Exp. Therapeut. Reperfusion Injury, Brigham and Women's Hosp. and Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: J. Biol. Chem. (1997), 272(11), 6972-6978
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

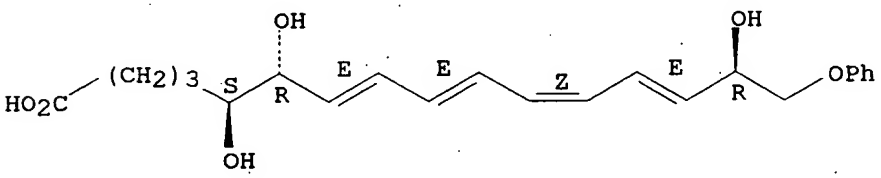
AB Lipoxins (LX) are bioactive eicosanoids that activate human monocytes and inhibit neutrophils. LXA4 is rapidly converted by monocytes to inactivate products, and to resist metab., synthetic analogs of LXA4 were designed. Here, the authors examd. the bioactivity of several LXA4 analogs in monocytes and found, for chemotaxis, 15(R/S)-methyl-LXA4 were equal in activity, and 16-phenoxy-LXA4 was more potent than native LXA4. Both 15(R/S)-methyl-LXA4 and 16-phenoxy-LXA4 were .apprx.1 log molar more

potent than LXA4 in stimulating THP-1 cell adherence (EC50 .apprxeq.1 .times. 10-10 M). Dimethylamide derivs. of the LXA4 analogs also possessed agonist rather than antagonist properties for monocytes. Neither LXA4 nor 16-phenoxy-LXA4 affected monocyte-mediated cytotoxicity. The authors cloned an LXA4 receptor from THP-1 cells identical to that found in PMN. Evidence of receptor-mediated function of LXA4 and the stable analogs in monocytes included desensitization of intracellular calcium mobilization to a second challenge by equimolar concns. of these analogs, but not to LTB4. Increases in [Ca2+]i by LXA4 and the analogs were specifically inhibited by an antipeptide antibody to the LXA4 receptor; and both LXA4- and analog-induced adherence and increments in Ca2+ were sensitive to pertussis toxin. Together, these results indicate that the LXA4 stable analogs are potent monocyte chemoattractants and are more potent than native LXA4 in stimulating THP-1 cell adherence, at subnanomolar concns. Moreover, they provide addnl. evidence that the LXA4 stable analogs retain selective bioactivity in monocytes and are valuable instruments for examg. the functions and modes of action of LXA4.

IT **171030-12-9 189005-35-4**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(lipoxin A4 stable analogs are potent mimetics that stimulate human monocytes and THP-1 cells via a G-protein-linked lipoxin A4 receptor)

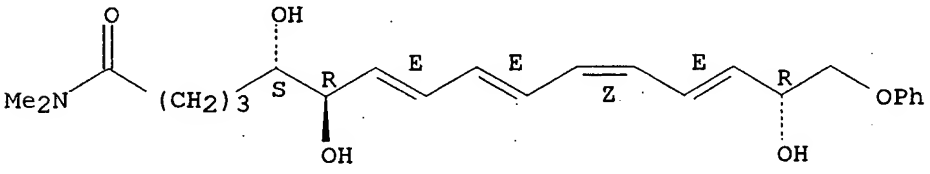
RN 171030-12-9 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 189005-35-4 CAPLUS
CN 7,9,11,13-Hexadecatetraenamide, 5,6,15-trihydroxy-N,N-dimethyl-16-phenoxy-, [5S-(5R*,6S*,7E,9E,11Z,13E,15S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L12 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:435841 CAPLUS
DOCUMENT NUMBER: 122:205187
TITLE: Lipoxin compounds for modulation of inflammation of columnar epithelia
INVENTOR(S): Madara, James L.; Serhan, Charles N.; Colgan, Sean P.
PATENT ASSIGNEE(S): Brigham and Women's Hospital, USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
Searched by Barb O'Bryen, STIC 308-4291

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9501179	A1	19950112	WO 1994-US7333	19940629
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9472152	A1	19950124	AU 1994-72152	19940629
PRIORITY APPLN. INFO.:			US 1993-84311	19930629
			WO 1994-US7333	19940629

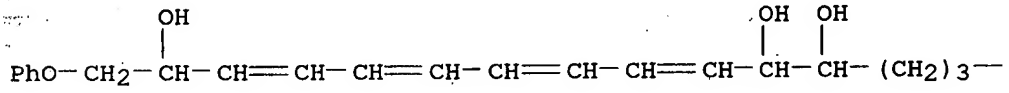
OTHER SOURCE(S): MARPAT 122:205187

AB A pharmaceutical compn. for treating or preventing a disease or condition assocd. with columnar epithelial inflammation or with abnormal transportation of fluids, electrolytes, or nutrients by a columnar epithelium contains lipoxin A4 or its analogs. Columnar epithelium is an epithelium of the intestine, kidney, stomach, liver, thyroid, trachea, lung, gall bladder, urinary bladder, bile duct, pancreatic duct, or testicle.

IT **161718-15-6 161718-22-5**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipoxin compds. as inflammation inhibitors for columnar epithelia)

RN 161718-15-6 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy- (9CI) (CA INDEX NAME)

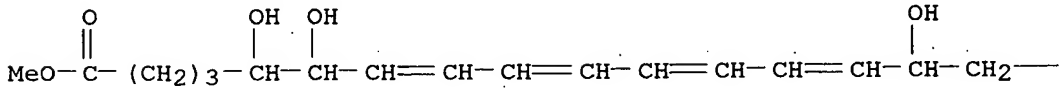
PAGE 1-A



PAGE 1-B

RN 161718-22-5 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, methyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

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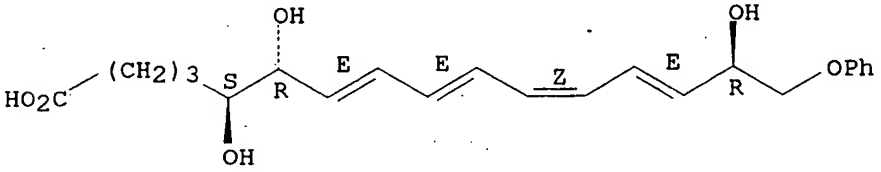
L12 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:875227 CAPLUS
DOCUMENT NUMBER: 124:213
TITLE: Design of Lipoxin A4 Stable Analogs That Block Transmigration and Adhesion of Human Neutrophils
AUTHOR(S): Serhan, Charles N.; Maddox, Jane F.; Petasis, Nicos A.; Akritopoulou-Zanze, Irini; Papayianni, Aikaterina; Brady, Hugh R.; Colgan, Sean P.; Madara, James L.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital, Boston, MA, 02115, USA
SOURCE: Biochemistry (1995), 34(44), 14609-15
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lipoxins (LX) are bioactive eicosanoids that carry a tetraene structure and serve as regulators of inflammation, in part by inhibiting neutrophil migration and adhesion. Lipoxin A4 is rapidly regulated by conversion to inactive LX metabolites via local metab. that involves dehydrogenation as the predominant route. Here, several LXA4 analogs were designed that resisted rapid conversion by both differentiated HL-60 cells and recombinant 15-hydroxyprostaglandin dehydrogenase, systems where native LXA4 is degraded within minutes. The rank order of conversion by recombinant dehydrogenase was LXA4 Me ester > PGE2 .apprxeq. PGE2 Me ester > LXA4 >>> the novel LXA4 analogs. In addn., 15(R/S)-methyl-LXA4, 15-cyclohexyl-LXA4, and 16-phenoxy-LXA4 proved to retain LXA4 bioactivity and inhibited neutrophil transmigration across polarized epithelial cell monolayers as well as adhesion to vascular endothelial cells. These results indicate that LXA4 analogs can be designed using these criteria to resist rapid transformation and to retain biol. actions of native LXA4. Moreover, the results suggest that LXA4 stable analogs can be useful tools both in vitro and in vivo to evaluate LXA4 actions and therapeutic potential.

IT **171030-12-9**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(design of lipoxin A4 stable analogs that block transmigration and adhesion of human neutrophils)

RN 171030-12-9 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



IT **171030-14-1**

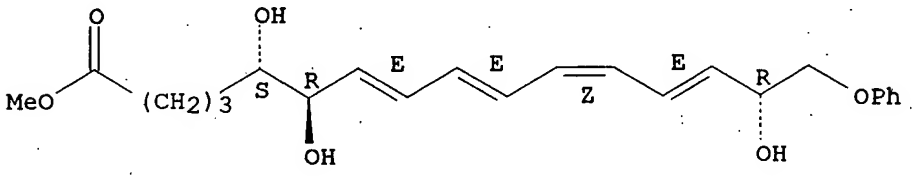
Searched by Barb O'Bryen, STIC 308-4291

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(design of lipoxin A4 stable analogs that block transmigration and adhesion of human neutrophils)

RN 171030-14-1 CAPLUS

CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, methyl ester, (5S,6R,7E,9E,11Z,13E,15R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L12 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:573821 CAPLUS

DOCUMENT NUMBER: 122:314353

TITLE: Lipoxin compounds

INVENTOR(S): Serhan, Charles N.

PATENT ASSIGNEE(S): Brigham and Women's Hospital, USA

SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

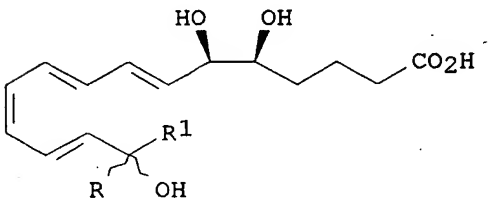
FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9429262	A1	19941222	WO 1994-US6822	19940615
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2164951	AA	19941222	CA 1994-2164951	19940615
AU 9471109	A1	19950103	AU 1994-71109	19940615
AU 692453	B2	19980611		
EP 703897	A1	19960403	EP 1994-920241	19940615
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08512023	T2	19961217	JP 1994-502216	19940615
PRIORITY APPLN. INFO.:			US 1993-77300	19930615
			WO 1994-US6822	19940615

OTHER SOURCE(S): MARPAT 122:314353

GI



I

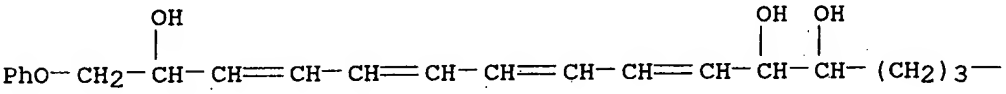
AB Compds. having the active site of natural lipoxins, but a longer tissue

half-life, in particular I [R = H, Me; R1 = pentyl, cyclohexyl, CH2OPh] and their 11,12-didehydro analogs are disclosed. These small mols. are useful for treating vasoconstrictive, inflammatory, myeloid suppressive, cardiovascular, and gastrointestinal diseases. Thus, I inhibited neutrophil adhesion to endothelial cells and polymorphonuclear cell adhesion to endothelial cells triggered by leukotriene B4. 1He acetylenic analogs of I were more stable than I.

IT **161718-15-6P 161718-22-5P**
RL: BAC (Biological activity or effector, except adverse); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(lipoxin analogs with longer tissue half-life)

RN 161718-15-6 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy- (9CI) (CA INDEX NAME)

PAGE 1-A



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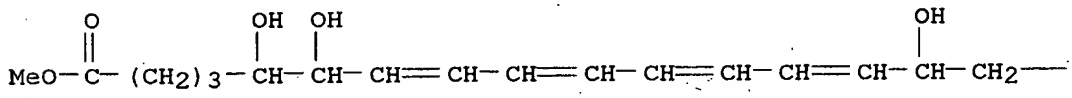
RN 161718-22-5 CAPLUS
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, methyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



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L12 ANSWER 23 OF 23 USPATFULL

ACCESSION NUMBER:	97:61839 USPATFULL
TITLE:	Lipoxin compounds
INVENTOR(S):	Serhan, Charles N., Boston, MA, United States
PATENT ASSIGNEE(S):	Brigham & Womens Hospital, Boston, MA, United States (U.S. corporation)

PATENT INFORMATION:	NUMBER	DATE
	US 5648512	19970715

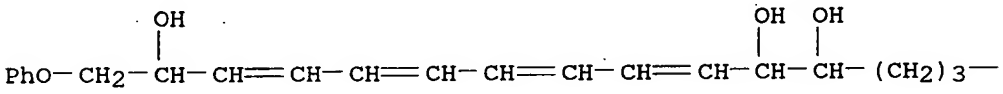
Searched by Barb O'Bryen, STIC 308-4291

APPLICATION INFO.: US 1995-453125 19950531 (8)
RELATED APPLN. INFO.: Division of Ser. No. US 1994-260030, filed on 15 Jun 1994, now patented, Pat. No. US 5441951 which is a continuation-in-part of Ser. No. US 1993-77300, filed on 15 Jun 1993, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Geist, Gary
ASSISTANT EXAMINER: Williams, Rosalynd
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 2197
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds having the active site of natural lipoxins, but a longer tissue hlf-life are disclosed. These small molecules are useful for treating vasoconstrictive, inflammatory, myeloid suppressive, cardiovascular, and gastrointestinal diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **161718-15-6P 161718-22-5P**
(lipoxin analogs with longer tissue half-life)
RN 161718-15-6 USPATFULL
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy- (9CI) (CA INDEX NAME)

PAGE 1-A



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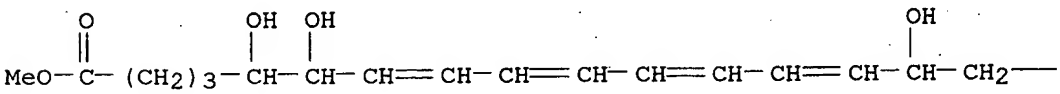
RN 161718-22-5 USPATFULL
CN 7,9,11,13-Hexadecatetraenoic acid, 5,6,15-trihydroxy-16-phenoxy-, methyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



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